REMARKS

Claims 1-3, 5-12, and 14-23 are pending herein. By this Amendment, Claims 4 and 13 are canceled without prejudice or disclaimer; Claims 1-3 and 18 are amended; and new Claims 22-23 are added. Support for the claim amendments and new claims is found in the specification at, *inter alia*, paragraphs [0036], [0047]-[0050], and [0065]. No new matter is added by this Amendment.

I. REJOINDER

Applicants respectfully request rejoinder of withdrawn Claims 7-12, 14, and 17 upon allowance of the pending claims.

II. FORMAL MATTERS

A. Enablement

Claims 1-6, 13, 15-16, and 18-21 were rejected under 35 U.S.C. 112, first paragraph, as assertedly being non-enabled. This rejection is respectfully traversed.

According to the present invention, if rodents at a contaminated site have impaired reproductive capability as determined by exceedances of sperm parameter benchmarks, then by implication, other site terrestrial ecological receptors, such as mammals, have the potential to be experiencing similar reduced reproductive success. Rodents are the "perfect real-world, worst-case receptors of exposure" because they burrow in the contaminated soil, eat contaminated vegetation, and drink contaminated water. They typically do not migrate and many generations of rodents live in contaminated areas year after year. See specification at paragraph [0036].

Based upon the results of the claimed Rodent Sperm Analysis (RSA), results can be extrapolated for other receptors, for example, regarding their contact with the ground and foraging (paragraph [0051]). Thus, if rodents are not experiencing reproductive

impacts, it can be reasoned that other receptors are also not experiencing compromised reproductive success. Thus, the specification provides a clear rationale as to how and why determining the risk to rodents may be extrapolated to assess the ecological risk to other animals.

It is axiomatic that the vast majority of our understanding of toxicity in animals and humans derives from testing with rodents. The article cited by the Examiner, Phillips et al. "Assessment of Potential Environmental Health Risks of High-Explosive Munitions in Military Test Ranges – Comparisons in a Humid and Arid Climate", shows that is it well known to model and estimate health effects and ecological risks using, for example, rodents.

In the Advisory Action dated October 16, 2007, the Examiner partially agreed, but argued that amphibians are more sensitive to environmental changes, so that a rodent model may not be applicable to all animals. As discussed with Examiner Lin in an October 31, 2007 telephone conference, the pending claims are amended to recite methods for assessing ecological risk to mammals, thereby excluding amphibians and avian species.

In the Advisory Action, the Examiner also asserts that, while Phillips et al. state that the rodent is a well known model, "they acknowledge that it is not necessarily an accurate model for all animals". Applicants respectfully disagree. Phillips et al. clearly discloses that it is known to estimate health risks to humans using rodents. Further, Phillips et al. merely discloses that in addition to using a rodent model, other models may also be used, such as deer and clams which are acknowledged along with rodents as being pathways of accumulation in the food chain. See page 15, first paragraph. Thus, Phillips et al. acknowledges several complementary models; obtains tissue samples from deer, rodents, vegetation, insects, and clams; and compares site results to background levels from references sites (page 16, second full paragraph).

See also Sample et al., Toxicological Benchmarks for Wildlife: 1996 Revision, Health Sciences Research Division (submitted concurrently with an Information Disclosure Statement), which indicates on page 3:

> In this report, benchmarks for mammalian species of wildlife have been estimated from studies conducted primarily on laboratory rodents, and benchmarks for avian species have been estimated from studies on domestic and wilds birds. Few experimental toxicity data are available for other groups of wildlife such as reptiles and amphibians, and it is not considered appropriate to apply benchmarks across different groups.

(Emphasis added).

One of ordinary skill in the art would be able to practice the claimed invention without undue experimentation. The pending claims are enabled and the requirements of 35 U.S.C. 112, first paragraph, are satisfied. Reconsideration and withdrawal of the rejection are respectfully requested.

B. New Matter

Claim 16 was rejected under 35 U.S.C. 112, first paragraph, as assertedly not having an adequate written description and/or reciting new matter. Paragraph [0051] supports the instant claim. In the Advisory Action, this rejection was withdrawn. Applicant respectfully notes that Claim 16 has not been rejected over any art of record and therefore should be indicated as allowed.

C. Indefiniteness

Claims 1-6, 13, 15-16, and 18-21 were rejected under 35 U.S.C. 112, second paragraph, as assertedly being indefinite. Claim 13 is canceled. This rejection is respectfully traversed with respect to the pending claims.

Independent Claims 1 and 18 are amended to clarify (1) comparing sperm analysis (e.g., sperm count, sperm motility, or sperm morphology) of rodents from a contaminated site with rodents from an animal reference site; and (2) determining whether the comparison between the sperm analysis of the rodents from the contaminated site and of the rodents from the animal reference site exceeds one or more sperm parameter benchmarks. Thus, Claims 1 and 18 do not omit any essential steps. As discussed above, one of ordinary skill in the art would be able to make a determination as to the ecological risk to or health of mammals based upon the reproductive impacts of rodents. The specification provides a clear rationale as to why determining the risk to rodents may be extrapolated to assess the ecological risk to or health of other mammals.

The scope of the pending claims would be reasonably ascertainable to one of ordinary skill in the art when read in light of the specification and drawings, thereby satisfying the requirements of 35 U.S.C. 112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

III. REJECTION UNDER 35 U.S.C. 102(b)

Claims 1-3 and 6 were rejected under 35 U.S.C. 102(b) as anticipated by Ieradi et al., *Genetic Damage in Urban Mice Exposed to Traffic Pollution*, Environmental Pollution, Vol. 92, No. 3, pp. 323-28 (1996).

Non-rejected Claim 4 is canceled and its subject matter is incorporated into independent Claim 1, thereby rendering the rejection moot. Reconsideration and withdrawal of the rejection are respectfully requested.

IV. REJECTIONS UNDER 35 U.S.C. 103(a)

Further to the October 31, 2007 telephone conference with Examiner Lin, the independent claims are amended to recite that the rodents of the contaminated site reflect generations of exposure to the contaminated site.

A. Claims 4-5, 13 and 18

Claims 4-5, 13 and 18 were rejected under 35 U.S.C. 103(a) as obvious over Ieradi et al. in view of Sharma et al., *Reversible Effects of Mercuric Chloride on Reproductive Organs of the Male Mouse*, Reproductive Toxicology, Vol. 10, No. 2, pp. 153-59 (1996). Claims 4 and 13 are canceled. This rejection is respectfully traversed with respect to the pending claims.

1. Ieradi et al. Does Not Teach or Suggest Sperm Parameter Benchmarks Indicating Impaired Reproductive Capability

Ieradi et al. discloses collecting rodents from three areas in Rome exposed to different traffic flows to ascertain a possible correlation between genetic damage and heavy metal concentration. A statistically significant increase in the frequency of abnormal sperm cells was obtained in animals collected in sites with high traffic flows (Abstract).

Ieradi et al. discloses sperm abnormalities of wild rodents and correlates the abnormal sperm count frequencies to contents of cadmium and lead in the kidney. Contrary to the Examiner's assertion, Ieradi et al. does not teach or suggest (1) obtaining a representative sample of rodents from a contaminated site, wherein the rodents reflect generations of exposure to the contaminated site; (2) comparing at least one result of the first sperm analysis of rodents from a contaminated site with at least one result of the second sperm analysis of rodents from an animal reference site; and (3) determining whether the comparison exceeds one or more sperm parameter benchmarks, thereby indicating if the rodents from the contaminated site have impaired reproductive capability or compromised reproductive success.

The Examiner asserts that "data from mice from the reference site may be viewed as the 'benchmark' for determining impaired reproductive capability of the mice"

(Office Action at page 9). This interpretation of "benchmark" is factually and scientifically incorrect and gives no patentable weight to the other features of the claimed invention.

As discussed in the specification at paragraph [0048] and at the February 22, 2007 personal interview, the sperm parameter benchmarks for impaired reproductive capability (i.e., thresholds-for-effect exceedances) do not simply correspond to data from a control group. For example, it may be determined that the rodents trapped at the contaminated site may have a lesser sperm count than from a reference location (i.e., control group). However, rodents are robustly fertile and thus sperm count needs to be reduced approximately 80% or more (sperm parameter benchmark) before reproductive success is compromised. As disclosed in paragraph [0048] of the specification:

> Thus, if a study reveals that sperm count in rodents trapped at the contaminated site is only reduced by forty percent when compared with the rodents of the uncontaminated reference location, for example, a threshold-for-effect will **not** have been shown to have been exceeded, and it cannot be determined that reproductive success will be compromised in these animals.

(Emphasis added). See also paragraphs [0007]-[0008], which disclose that simply comparing animal tissues of a chemically-contaminated site and a non-contaminated site is inadequate to assess ecological risk and health effects.

Moreover, Ieradi et al. does not teach or suggest that the comparison between lead, cadmium, and zinc levels and abnormal sperm cells between different groups of rodents has anything to do with impaired reproductive capability. Ieradi et al. merely discloses earmarks to document exposure to pollutants – that is, the mice are simply bioindicators to detect local contamination.

Applicant also respectfully notes that the language "threshold-for-effect exceedances" was discussed at the interview and it was suggested to clarify this language as relating to sperm parameters benchmarks for impaired reproductive

capability or compromised reproductive success. See Interview Summary dated 22 February 2007.

2. Sharma et al. In Combination With Ieradi et al. Do Not Teach or Suggest the Claimed Sperm Parameter Benchmarks Indicating Impaired Reproductive Capability

Sharma et al. does not overcome the deficiencies of Ieradi et al. Sharma et al. discloses the effects of oral administration of mercuric chloride ($HgCl_2$) on mouse testis, vas deferens, epididymis, and cauda epididymal sperm and recovery after withdrawal of $HgCl_2$. Testis, vas deferens, and epididymis functions were evaluated with respect to sperm count, sperm motility, and viability (Abstract).

Sharma et al. discloses the absolute toxic effects of mercury and recovery after withdrawal of mercury. There is no teaching of correlating lab-imposed, Hg-mediated effects to the ecological risk to animals at a contaminated site using impaired reproductive capability or compromised reproductive success of rodents as a toxicological endpoint.

Like Ieradi et al., Sharma et al. does not teach or suggest (1) obtaining a representative sample of rodents from a contaminated site, wherein the rodents reflect generations of exposure to the contaminated site; (2) comparing at least one result of the first sperm analysis of rodents from a contaminated site with at least one result of the second sperm analysis of rodents from an animal reference site; and (3) determining whether the comparison exceeds one or more sperm parameter benchmarks, thereby indicating if the rodents from the contaminated site have impaired reproductive capability or compromised reproductive success.

Further, the Examiner's reasoning for motivation to combine the two references is to "determine pollution at a site" (Office Action at page 11). However, the claimed invention is not directed to detecting level of pollution at a contaminated site, but rather to assessing whether a site poses an ecological risk to animals in view of exceedances

of rodent sperm parameter benchmarks and a determination of impaired reproductive capability.

Thus, it would not have been obvious for one of ordinary skill in the art to practice the claimed methods in view of the combined teachings of Ieradi et al. and Sharma et al. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claim 15

Claim 15 was rejected under 35 U.S.C. 103(a) as being unpatentable over Ieradi et al. in view of Sharma et al. and further in view of Phillips et al. This rejection is respectfully traversed.

Phillips et al. does not overcome the deficiencies of Ieradi et al. and Sharma et al. Phillips et al. discloses estimating health risks associated with exposure to munitions residues. Although Phillips et al. collected data from rodents,

> Rodent, vegetation, and insect tissue were sampled at YPG for metals and explosives. Again, no explosives were found in any of the tissue. The metals found were all within the background range for each respective biological organism. We found a similar situation at APG for biological organisms.

(Page 18, emphasis added).

There is no reason to apply the teachings of Phillips et al. with Ieradi et al., since Phillips et al. indicates that rodents are not bioindicators for explosives or metals, as required by Ieradi et al. Again, there is a great difference between (1) simply analyzing tissue as disclosed in Phillips et al. or analyzing sperm as disclosed in Ieradi et al. and Sharma et al. and (2) assessing ecological risk using impaired reproductive capability of rodents according to the present invention.

Ieradi et al., Sharma et al., and Phillips et al., alone or in combination, do not teach or suggest (1) obtaining a representative sample of rodents from a contaminated

site, wherein the rodents reflect generations of exposure to the contaminated site; (2) comparing at least one result of the first sperm analysis of rodents from a contaminated site with at least one result of the second sperm analysis of rodents from an animal reference site; and (3) determining whether the comparison exceeds one or more sperm parameter benchmarks, thereby indicating if the rodents from the contaminated site have impaired reproductive capability.

Thus, it would not have been obvious for one of ordinary skill in the art to practice the claimed methods in view of the combined teachings of Ieradi et al., Sharma et al., and Phillips et al. Reconsideration and withdrawal of the rejection are respectfully requested.

C. Claim 19

Claim 19 was rejected under 35 U.S.C. 103(a) as being unpatentable over Ieradi et al. in view of Sharma et al. and further in view of Meistrich et al. This rejection is respectfully traversed.

Meistrich et al. does not overcome the deficiencies of Ieradi et al. and Sharma et al. Meistrich et al. compares the fecundity of *azh* mutation male mice to wild-type or heterozygous animals (page 74, Discussion). In normal rodents, busulfan-induced reductions in sperm counts to between 10% and 50% reduce litter size only from 6.3 to 4.9 births/litter (page 75, left hand column). Busulfan is a particular chemical known to adversely affect spermatogenesis. See Bucci et al., "Effects of busulfan on murine spermatogenesis: cytotoxicity, sterility, sperm abnormalities, and dominant lethal mutations" (filed with an Information Disclosure Statement).

Like Sharma et al., Meistrich et al. refers to analysis of lab-induced administration of a single chemical to determine the absolute toxic effects, for example, on sperm count. There is no recognition or appreciation that the lab-induced data of Sharma et al. and/or Meistrich et al. is even applicable to real-world contaminated sites. Any

combination of Sharma et al. and Meistrich et al. with Ieradi et al. would at best result in using mice as bioindicators for the presence of mercury and busulfan in addition to the heavy metals disclosed in Ieradi et al.

There is simply no teaching or suggestion in the combined teachings of the cited references to: (1) obtain a representative sample of rodents from a contaminated site, wherein the rodents reflect generations of exposure to the contaminated site; (2) compare sperm count, sperm motility, and sperm morphology of the rodents from the contaminated site with the rodents from the animal reference site; and (3) determine whether the comparison between the sperm count, sperm motility, or sperm morphology of the rodents from the contaminated site and of the rodents from the animal reference site exceeds one or more sperm parameter benchmarks, thereby indicating if the rodents from the contaminated site have compromised reproductive success and making a determination about the health of terrestrial site animals at the contaminated site.

Thus, it would not have been obvious for one of ordinary skill in the art to practice the claimed methods in view of the combined teachings of Ieradi et al., Sharma et al., and Meistrich et al. Reconsideration and withdrawal of the rejection are respectfully requested.

D. Claims 20-21

Claims 20-21 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ieradi et al. in view of Sharma et al. and further in view of Chapin et al. This rejection is respectfully traversed.

Chapin et al. does not overcome the deficiencies of Ieradi et al. and Sharma et al. Chapin discloses the effects on reproduction by exposing mice to chemicals. According to Chapin, sperm abnormality rates of greater than or equal to 16% were associated with reduced fertility (page 131, left hand column). Chapin also discloses that normal

fertility was maintained in treated animals until motility declined to approximately 40-50% (page 131, right hand column).

Chapin et al. refers to analysis of lab-induced administration of chemicals to determine the absolute toxic effects. There is no recognition or appreciation that such lab-induced data of Sharma et al. and/or Chapin et al. is applicable to real-world contaminated sites. Any combination of Sharma et al. and Chapin et al. with Ieradi et al. would at best result in using mice as bioindicators for the presence of other chemicals and examining the absolute toxic effects of such chemicals.

There is simply no teaching or suggestion in the combined teachings of the cited references to: (1) obtain a representative sample of rodents from a contaminated site, wherein the rodents reflect generations of exposure to the contaminated site; (2) compare sperm count, sperm motility, and sperm morphology of the rodents from the contaminated site with the rodents from the animal reference site; and (3) determine whether the comparison between the sperm count, sperm motility, or sperm morphology of the rodents from the contaminated site and of the rodents from the animal reference site exceeds one or more sperm parameter benchmarks, thereby indicating if the rodents from the contaminated site have compromised reproductive success and making a determination about the health of terrestrial site animals at the contaminated site.

Thus, it would not have been obvious for one of ordinary skill in the art to practice the claimed methods in view of the combined teachings of Ieradi et al., Sharma et al., and Chapin et al. Reconsideration and withdrawal of the rejection are respectfully requested.

V. CONCLUSION

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone

interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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